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BY

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THE CONSTITUTION OF EVODIONOL.

By F. N. LAHEY, D.Sc., A.A.C.I.

In a previous paper[1] the results of some degradation experiments on evodionol were recorded and the suggestion made that that substance contained a benzopyran nucleus. Further evidence to support this has now been obtained and the constitution of evodionol definitely established. The present paper modifies some conclusions drawn in the previous paper and also presents the evidence for the constitution of evodionol including a synthesis of dihydro-methyl-evodionol.

The yellow colour of evodionol which disappears on methylation suggests that the phenolic hydroxyl group is in the ortho position to the carbonyl group. This arrangement has been confirmed by the formation of copper derivatives of the oximes of evodionol and dihydro-evodionol. The formation of copper derivatives of oximes was shown by Ephraim[2] to be characteristic of the arrangement $-\overset{\|}{\underset{NOH}{C}}-\overset{|}{C}-\overset{|}{C}-OH$, a property used by Cousin and Lions[3] to establish the presence of this arrangement.

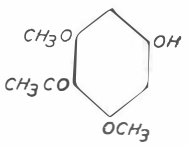
Previously the presence of a C-acetyl group had been accepted due to the formation of bromoform by hypobromite treatment of the dibasic acid obtained by oxidation of methyl-evodionol. An unsuccessful attempt was made to establish directly the presence of this group by a method used by Kamthong and Robertson[4] in the study of euparin. The method involved the Beckmann rearrangement of the oxime of dihydro-methyl-evodionol followed by hydrolysis of the amide to the amine and conversion back to the amide by acetylation. Although in this case the oxime readily underwent the Beckmann rearrangement to form the amide, the steric effects operating resulted in only a very small amount of an amine being formed on hydrolysis. Insufficient was obtained for analyses and conversion back to the amide by acetylation. The presence of the C-acetyl group was readily established, however, by its identification in degradation products to be described.

From preliminary experiments described in the previous paper it appeared that further examination of the products of pyrolysis of the dibasic acid $C_{15}H_{18}O_8$ formed by oxidation of methyl evodionol, would give a valuable lead to the constitution of evodionol. On being heated to 140-150° the dibasic acid, which will be referred to in future as evodionic acid, yielded a trace of acetic acid and an acid which would not crystallise but set to a glass-like mass. On esterification this acid gave a reasonable yield of the solid methyl ester, m.p. 76°C., normally obtained by esterification of evodionic acid. In addition a small amount of a solid, m.p. 185° C., insoluble in bicarbonate, soluble in carbonate and giving no colour with ferric chloride was isolated from the products of pyrolysis. This has been identified as 4-hydroxy-2 : 6-dimethoxy-acetophenone (1) by conversion into O-trimethyl phloracetophenone by methylation and by comparison with a synthetic sample prepared by the method of Canter, Curd and Robertson[5]. Its behaviour towards bicarbonate and carbonate solutions seems to be characteristic of phenols having a carbonyl group in the para position to the phenolic hydroxyl group (compare decarbousnic acid, Curd and Robertson[6].)

By raising the temperature of pyrolysis, of either evodionic acid or the glassy acid from the above pyrolysis, a phenol O-dimethyl phloroglucinol is obtained which on methylation gives O-trimethyl-phloroglucinol, m.p. 51°-52°. The formation of

4-hydroxy-2 : 6-dimethoxy-acetophenone and O-dimethyl phloroglucinol can readily be explained on the basis of a benzopyran nucleus in methyl-evodionol. Also the relative position of the methoxyl and carbonyl groups on such a nucleus are simultaneously determined.

Only two carbon atoms remain to be accounted for if a benzopyran ring is assumed. As these are not attached to the benzene nucleus the only position in which to place them so as to have no asymmetric carbon atom and to account for the formation of a dibasic acid $C_{15}H_{18}O_8$ by oxidation of methyl-evodionol without loss of carbon, is on carbon atom 2. A possible formula for a methyl-evodionol on this evidence is given by (2).



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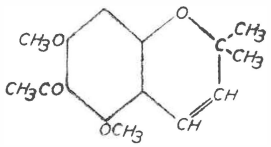

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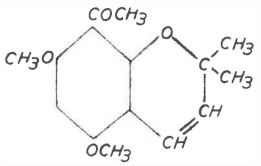
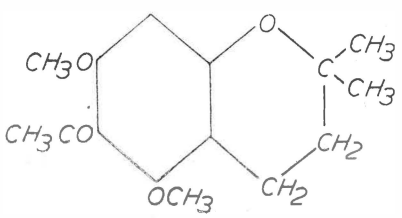


3

Robertson and co-workers[7] have recently investigated a number of substances containing the 2 : 2-dimethyl benzopyran nucleus and have formed a qualitative test for this nucleus which has been successful in all cases tried where positions (3) and (4) are unsubstituted. The test consists of the recognition of acetone, by means of its 2 : 4 dinitro-phenyl-hydrazone, as the steam volatile product of the action of strong caustic soda on the 2 : 2-dimethyl-benzopyran. This test applied to evodionol gave positive results while dihydro evodionol in which the pyran nucleus is reduced failed to yield any acetone. These results support the 2 : 2 dimethyl-benzopyran formula. The identification of (1) as a degradation product of methyl evodionol also necessitates placing the C-acetyl group in position 6 for if placed in position 8, the only other position available, as in formula (3) any phenol obtained by decomposition of the corresponding dibasic acid would be an ortho-hydroxy ketone.

Furthermore, on reduction with hydrogen in the presence of platinum oxide, methyl-evodionol gives dihydro-methyl-evodionol which is accounted for by reduction of the double bond in the benzopyran nucleus. On the basis of formula (2) for methyl-evodionol, dihydro-methyl-evodionol must be 5 : 7 dimethoxy-6-acetyl-2 : 2-dimethyl-chroman (4).



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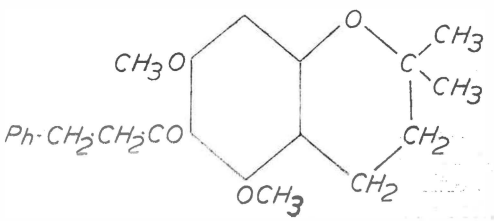
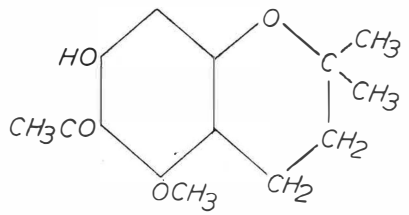


5

This readily gives a benzylidene derivative which on reduction gives the corresponding β-phenyl-propionyl compound (5). This is an oil which is characterised by the formation of an oxime m.p. 129·5° C. Backhouse and Robertson[8] have prepared

5 : 7-dimethoxy-6-β-phenyl-propionyl-2 : 2-dimethyl-chroman and record the same properties as the above, further supporting the view that the C-acetyl group is located at position 6 and not 8 on the nucleus.

Further evidence on this point was obtained indirectly. Dihydro-evodionol must be represented by either formula (6) or (7).



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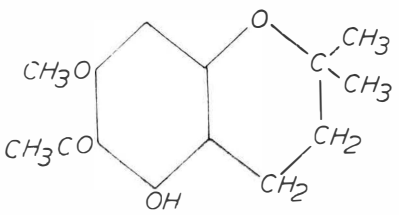
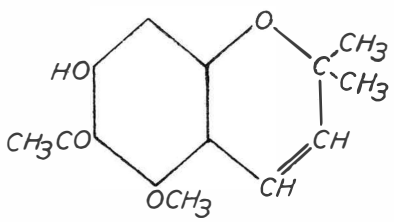


7

The 5-methyl ether of the corresponding 8-acetyl compound has been prepared synthetically by Backhouse and Robertson[8] and its properties do not agree with those of dihydro-evodionol. The 7-methyl ether of the 8-acetyl compound would not give a ferric chloride reaction. Dihydro-evodionol gives a brilliant red colour with ferric chloride.

Evodionol must therefore be either 7-hydroxy-5-methoxy-6-acetyl-2 : 2-dimethyl-1 : 2-benzopyran (8) or 5-hydroxy-7-methoxy-6-acetyl-2 : 2-dimethyl-1 : 2-benzopyran (9).



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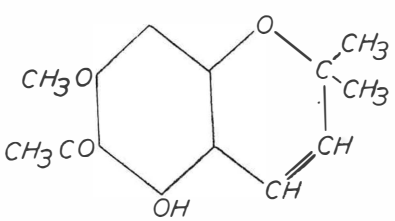
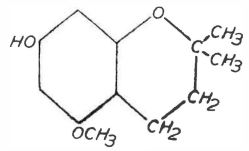


9

Evodionol and dihydro-evodionol were found to give negative results with 2 : 6-dibromquinone-chlorimide which would be expected if formula (8) were correct whereas a substance of formula (9) would be expected to yield a colour. Furthermore evodionol and dihydro-evodionol yield a dinitro and a mono-nitro derivative respectively when treated with concentrated nitric acid in alcohol. It is reasonable to assume that the only remaining position on the benzene nucleus, position 8, is the point of attack while in the case of evodionol the second nitro group must be attached to either carbon 3 or 4 as no substituent groups are lost during the nitration. It is clear then that an ortho-nitro phenol or a para-nitro phenol will be formed depending on whether evodionol is represented by formula (8) or (9.). Similarly in the case of dihydro-evodionol a substance of formula (6) would give an ortho-nitro phenol and of formula (7) a para-nitro phenol. By preparing equimolecular strength solutions in dilute alkali of nitro-dihydro-evodionol, dinitro-evodionol, ortho-nitro phenol and para-nitro phenol and comparing their colours (*see* Hantzsch[9]) confirmation of formula (8) for evodionol and (6) for dihydro-evodionol was obtained.

Further evidence in support of formula (8) was obtained by submitting the tetrahydro derivative of benzylidene-evodionol to drastic treatment with concentrated aqueous-alcoholic caustic potash. This yielded β-phenyl-propionic acid and a phenol, $C_{12}H_{10}O_3$ m.p. 103° C. which must be either 7-hydroxy-5-methoxy-2 : 2-dimethyl-chroman (10) or 5-hydroxy-7-methoxy-2 : 2-dimethyl-chroman (11). Both of these substances have been prepared by George and Robertson[10] who found that the former was a solid, m.p. 103-104° C. and the latter a reddish brown oil.



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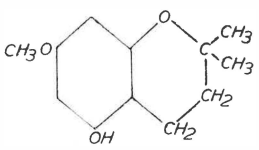

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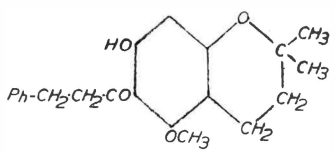
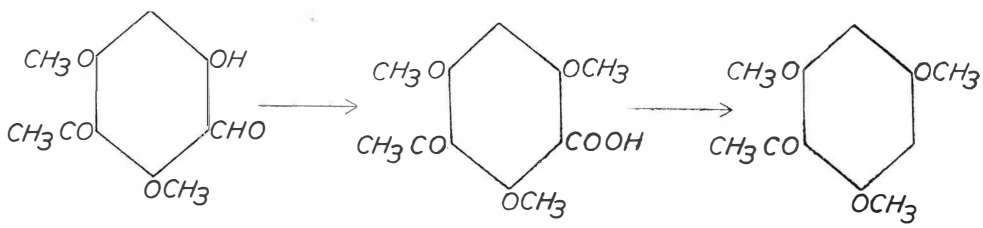


12

It is clear that tetrahydro-benzylidene-evodionol which was also formed by reduction of the benzylidene derivative of dihydro-evodionol must be 7-hydroxy-5-methoxy-6-β-phenyl-propionyl-2 : 2-dimethyl-chroman (12) in order to yield (10) on alkali treatment and that dihydro-evodionol and evodionol must be represented by formulae (6) and (8) respectively. In connection with the formation of 7-hydroxy-5-methoxy-6-β-phenyl-propionyl-2 : 2-dimethyl-chroman (12) it is of interest to note that this substance is insoluble in 1% caustic soda solution and gives a brilliant red ferric chloride reaction, properties which Backhouse and Robertson[8] predicted but did not prove because of the difficulty of partially methylating the corresponding dihydroxy compound. The properties of this substance thus confirm the reliability of the tests on which they base the identification of two isomeric substances, 5 : 7-dihydroxy-6-β-phenyl-propionyl-2 : 2-dimethyl-chroman and 5 : 7-dihydroxy-8-β-phenyl-propionyl-2 : 2-dimethyl-chroman.

Ozonolysis of methyl-evodionol gave interesting results, the principal product being a phenolic aldehyde $C_{11}H_{12}O_5$ having the properties of an ortho-hydroxy aldehyde and giving an intense red colour with ferric chloride. This was shown to be 6-hydroxy-2 : 4-dimethoxy-5-acetyl-benzaldehyde (13) for by methylation followed by oxidation it was converted to an acid $C_{12}H_{14}O_6$ (14) which readily decomposed at its melting point to yield O-trimethyl-phloraceto phenone (15).

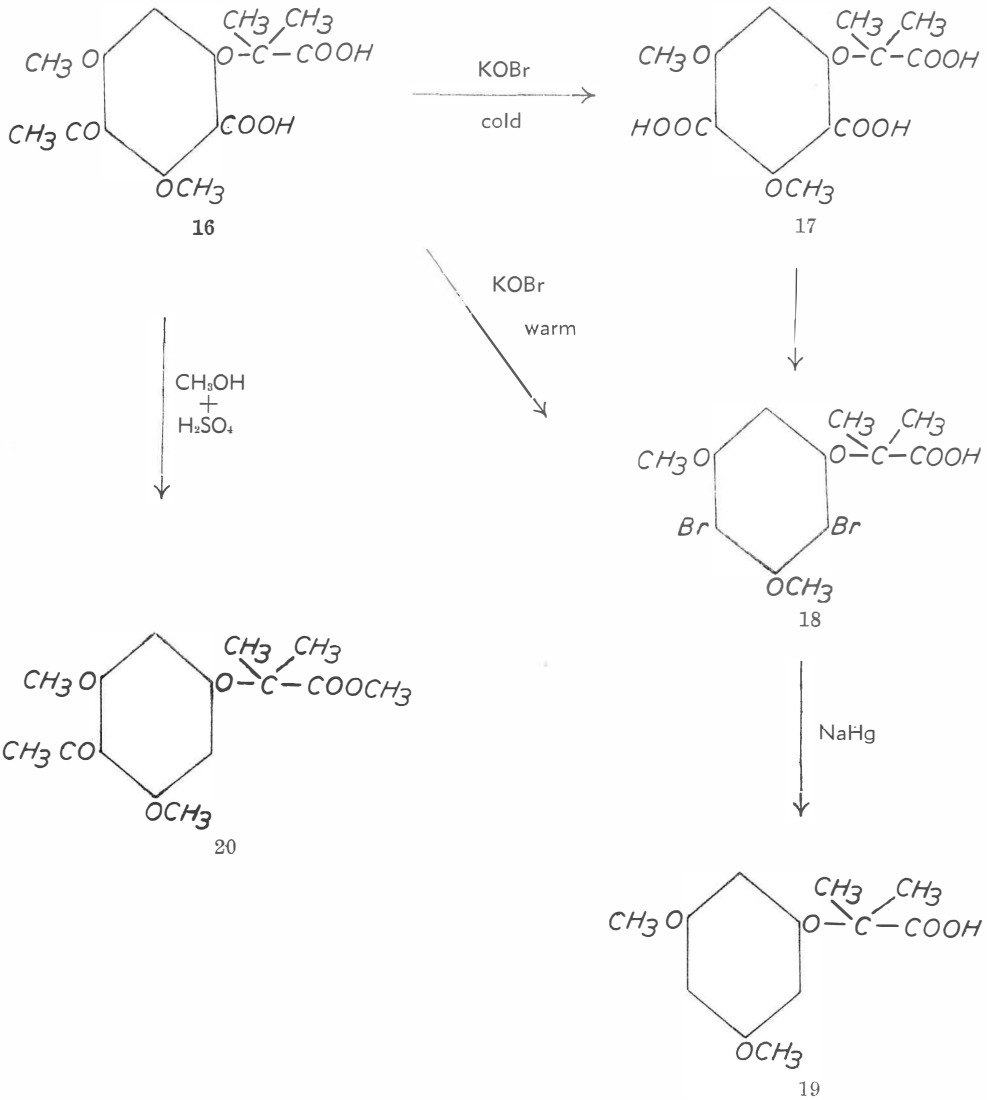


13 14 15

The loss of four carbon atoms with the formation of an ortho-hydroxy-aldehyde on ozonolysis of a 2 : 2-dimethyl-benzopyran nucleus has been observed before by Bell and Robertson[11] in the oxidation if xanthyletin.

It has been recorded in a previous publication that evodionol on oxidation with acetone permanganate yields a dibasic acid, evodionic acid, $C_{15}H_{18}O_8$ (16) without loss of carbon atoms. This acid on treatment with potassium hypobromite gives either a tribasic acid (17) or a dibromo-mono-basic acid (18), depending on the conditions

of the experiment (*see* previous paper[1]). Due to the ease with which the bromine atoms are removed with sodium amalgam it was thought that they must be located in a side chain and not on the nucleus. It is clear now that this is not so and that the only way to represent the above reaction is as follows :—



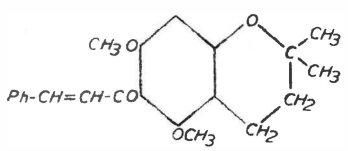
16 17 18 19 20

The last reaction with sodium amalgam affords an excellent example of the facile removal of halogen from the benzene nucleus, treatment for one hour with sodium amalgam in the cold being sufficient. Haworth, Perkin and Stevens[12] have removed halogens from the benzene nucleus in the same manner though in their case with less ease. The constitution of the final product α (3 : 5-dimethoxy-phenoxy-) isobutyric acid (19) was finally established by synthesis. This was accomplished by the condensation of methyl-α-bromisobutyrate and O-dimethyl-phloroglucinol with sodium ethoxide, followed by hydrolysis of the resulting ester. The synthetic

acid was found by mixed melting point determination to be identical with that obtained by degradation of methyl-evodionol. By strongly heating this acid with soda lime in an attempt to decarboxylate it, a neutral oil was obtained which partly solidified. This solid, obtained in very small amount, melted at 51° C. (incorrectly recorded as 54° C. in the previous paper) and was identified as O-trimethyl-phloroglucinol. Its formation from the acid (19) represents an unusual decomposition in which decarboxylation is accompanied by loss of two carbons with the formation of a methoxyl group from $-O-C(CH_3)_2-COOH$. The oil occupying the bulk of the product of the soda lime treatment was probably the normal decarboxylation product viz. 1 : 3-dimethoxy-5-isopropoxy-benzene, for this substance, prepared synthetically from O-dimethyl-phloroglucinol and isopropyl iodide, was obtained as an oil which has not been induced to crystallise. It is of interest to note that the acid α (3 : 5-dimethoxy-4-acetyl-phenoxy)-isobutyric acid from the ester (20) yields the same O-trimethyl-phloroglucinol on treatment with soda lime, in this case the C-acetyl group being simultaneously removed.

The constitution of the mono-methyl ester (20) which is formed together with carbon dioxide by the action of methyl alcohol and sulphuric acid on evodionic acid has been confirmed by its synthesis. Methyl α-brom-isobutyrate was made to condense with 4-hydroxy-2 : 6-dimethoxy-acetophenone (1) in the presence of potassium carbonate in acetone solution. A poor yield of ester was obtained identical with the ester derived from evodionic acid.

Oxidation of benzylidene-dihydro-methyl-evodionol (21) in acetone with cold aqueous permanganate gave an acid $C_{15}H_{18}O_6$ m.p. 169-170° C. (decomp.) which had the properties of an α-ketonic acid and must be represented by (22). On steam distillation in the presence of sulphuric acid it yielded a neutral oil containing no reactive groups and presumably therefore 5 : 7-dimethoxy-2 : 2-dimethyl-chroman. Analyses supported this conclusion. This substance has previously been obtained as an oil by Robertson and Subramaniam[13]. Its identity was confirmed by the formation of the 8-formyl derivative characterised by a semicarbazone and 2 : 4-dinitro-phenyl-hydrazone.



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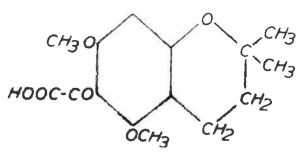

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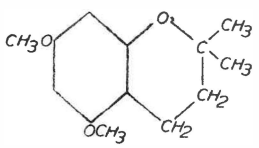
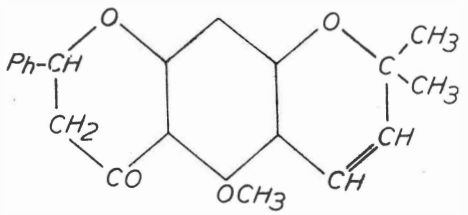


23

The benzylidene derivatives of the evodionol series have been found to be beautifully crystalline, readily prepared substances considered very useful for characterisation purposes. In the experimental section of this paper these and other simple derivatives not previously recorded are listed. Among these particular mention may here be made of the flavanones, 5-methoxy-8 : 8-dimethyl-1 : 2-pyrano-[3, 2, g]-flavanone (24) and 5-methoxy-8 : 8-dimethyl-6 : 7-dihydro-1 : 2-pyrano-[3, 2, g]-flavanone (25) formed from the corresponding benzylidene derivatives by refluxing with 10% sulphuric acid. These substances, prepared principally for spectrographic work recorded in the adjoining paper, are of particular interest because of their structural relationship to the naturally occurring substance isorottlerin recently studied by McGookin, Robertson and Tittensor[14].



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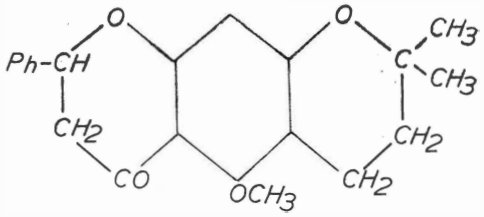

25

The degradative work just described leaves little doubt that the formula of evodionol is 7-hydroxy-5-methoxy-6-acetyl-2 : 2-dimethyl-1 : 2-benzopyran and that on reduction to dihydro-evodionol the benzopyran nucleus is reduced giving 7-hydroxy-5-methoxy-6-acetyl-2 : 2-dimethyl-chroman. As the final proof of any constitutional formula lies in synthesis, synthetic experiments in the evodionol series have been carried out. The synthesis of evodionol itself presents unusual difficulties which have not yet been overcome. However the synthesis of dihydro-methyl-evodionol and of the isomer of dihydro-evodionol, 5-hydroxy-7-methoxy-6-acetyl-2 : 2-dimethyl-chroman, have been accomplished. The first stage of the synthesis consisted of the preparation of 5 : 7-dihydroxy-2 : 2-dimethyl-chroman from the corresponding chromanone (Bridge, Heyes and Robertson[15]). The $\beta\beta$-dimethyl-acrylic acid necessary for the preparation of the chromanone was made by the method of Barbier and Leser consisting of the oxidation of mesityl oxide with sodium hypochlorite, a method much to be preferred to that used by Bridge, Heyes and Robertson. The acetyl group was then introduced by the Hoesch method and the 6-acetyl compound separated from the isomeric 8-acetyl compound by a slight modification of the method used by Backhouse and Robertson[8]. Methylation of the 6-acetyl compound with methyl iodide and potassium carbonate in acetone brought about the formation of a mono-methyl ether m.p. 88° C. It was anticipated that the 7-hydroxyl group would be more reactive towards methylating agents than the 5-hydroxyl so that the expected isomer of dihydro-evodionol, viz. 5-hydroxy-7-methoxy-2 : 2-dimethyl-chroman (7) was obtained. The structure of this is supported by the fact that, unlike dihydro-evodionol, it gives a brilliant colour with 2 : 6-dibrom-quinone-chlorimide, indicating an unsubstituted position para to the free hydroxyl group. Complete methylation was found difficult but by prolonged treatment with dimethyl sulphate and potassium carbonate in acetone the dimethyl ether was formed and found identical with dihydro-methyl-evodionol.

EXPERIMENTAL.

Derivatives of Evodionol

Evodionol oxime. Difficulty was experienced in forming the oxime by the normal procedure. Recourse was had to a method used by Cousin and Lions[3] which gave excellent results. Evodionol (·5 grm.) in alcohol (30cc.) was refluxed for eight hours in the presence of hydroxylamine hydrochloride (4 grms.) and barium carbonate (excess). At the end of that time the barium carbonate was filtered from the hot solution and the filtrate poured into water (100cc.). The oxime was extracted with ether, the extract dried and the ether distilled. The remaining oil slowly solidified and was crystallised from light petroleum. The oxime melted at 89° C. and gave a green colour with ferric chloride.

Found	C 63·8	H 6·5	N 5·7
Calc. for $C_{14}H_{17}NO_4$	C 63·8	H 6·5	N 5·3

Copper derivative of evodionol oxime. Evodionol oxime (·2 grm.) dissolved in glacial acetic acid (2cc.) was added to 5cc. of a solution of copper acetate in glacial

acetic acid. The brown precipitate which immediately formed was washed with acetic acid and then water.

Found	Cu 13·4
Calc. for $(C_{14}H_{16}O_4N)_2Cu$	Cu 13·6

Benzylidene-evodionol (7-hydroxy-5-methoxy-6-cinnamoyl-2 : 2-dimethyl-1 : 2-benzopyran.)

Evodionol (2 grms.) was dissolved in alcohol (50cc.) and to this solution was added benzaldehyde (2 grms.) and 2% caustic soda (40 cc.). This mixture was shaken for several hours and then allowed to stand overnight. On acidification a bright red oil separated which slowly solidified. It crystallised from alcohol in the form of brilliant red needles m.p. 94° C. It gave a brown colour with ferric chloride.

Found	C 75.	H 6·1
Calc. for $C_{21}H_{20}O_4$	C 75.	H 5·9

DERIVATIVES OF DIHYDRO-EVODIONOL.

Formed by the acetic anhydride, sodium acetate method the acetate of dihydro-evodionol melted at 84-85° C. after crystallisation from alcohol.

Dihydro-evodionol oxime. The same procedure was adopted as in the preparation of evodionol oxime. The oxime was obtained as white needles from dilute methyl alcohol. It melted at 132° C. and gave a violet colour with ferric chloride.

Found	C 63.	H 7·3	N 5·5
Calc. for $C_{15}H_{19}NO_4$	C 63·4	H 7.2	N 5·3

Copper derivative of dihydro-evodionol oxime. This was obtained as a brown precipitate under the same conditions used with evodionol oxime.

Found	Cu 13·2
Calc. for $(C_{14}H_{18}O_4N)_2Cu$	Cu 13·5

Three other derivatives of dihydro-evodionol which can be used for characterisation purposes are the 2 : 4-dinitro-phenyl-hydrazone and the mono-nitro and benzylidene derivatives. The 2 : 4-dinitro-phenyl-hydrazone formed by Brady's method was found to be almost insoluble in alcohol but readily crystallised from ethyl acetate in red needles m.p. 188° C.

Nitro-dihydro-evodionol. Dihydro-evodionol (1 grm.) in alcohol (10cc.) was added to a mixture of alcohol and nitric acid (4 : 1) (100cc.). The mixture was boiled gently for ten minutes and then poured into 200cc. of water. The solid product, mono-nitro-dihydro-evodionol, crystallised from alcohol (charcoal) in pale yellow needles m.p. 158·5° C.

Found	N 4·8
Calc. for $C_{14}H_{17}NO_6$	N 4·7

Benzylidene-dihydro-evodionol (*7-hydroxy-5-methoxy-6-cinnamoyl-2 : 2-dimethyl-chroman*).

Prepared in the usual way this derivative was obtained in the form of orange plates from alcohol m.p. 118° C. With ferric chloride it gave a red colour.

Found	C 74·3	H 6·6
Calc. for $C_{21}H_{22}O_4$	C 74·6	H 6·5

DERIVATIVES OF METHYL EVODIONOL.

The 2 : 4-dinitro-phenyl-hydrazone m.p. 157°C. was recorded in the previous paper[1]. The oxime formed by the method of Cousin and Lions (*loc. cit.*) crystallised from alcohol in squat prisms m.p. 135° C.

Found	C 64·8	H 6·8	N 5·2
Calc. for $C_{15}H_{19}NO_4$	C 65·	H 6·8	N 5·1

Benzylidene-methyl-evodionol (5 : 7-*dimethoxy*-6-*cinnamoyl*-2 : 2-*dimethyl*-1 : 2-*benzopyran.*)

This was prepared by dissolving methyl-evodionol (2 grams) in alcohol (50cc.) and to this adding benzaldehyde (2 grms.) and 2% caustic soda (40cc.). The mixture was vigorously shaken for several hours by which time a yellow oil had separated. This slowly solidified and crystallised from alcohol in fine yellow needles m.p. 114° C.

Found	C 75·4	H 6·3
Calc. for $C_{22}H_{22}O_4$	C 75·4	H 6·3

DERIVATIVES OF DIHYDRO-METHYL-EVODIONOL.

The 2 : 4-dinitro-phenyl-hydrazone of dihydro-methyl-evodionol in orange crystals m.p. 169°C.

Benzylidene-dihydro-methyl-evodionol (5 : 7-dimethoxy-6-cinnamoyl-2 : 2-dimethyl-chroman) was formed in the same way as benzylidene-methyl-evodionol. It crystallised from alcohol in yellow needles m.p. 104° C.

Found	C 75·	H 6·7
Calc. for $C_{22}H_{24}O_4$	C 75·	H 6·8

Dihydro-methyl-evodionol oxime crystallised from alcohol in colourless prisms m.p. 160-161° C.

Found	C 64·2	H 7·4	N 5·1
Calc. for $C_{15}H_{21}NO_4$	C 64·5	H 7·5	N 5·

Beckmann rearrangement of dihydro-methyl-evodionol oxime.

Dihydro-methyl-evodionol oxime was submitted to treatment with thionyl chloride according to the method used by Kamthong and Robertson (*loc. cit.*) in the investigation of the constitution of euparin. The pale pink amide obtained by the Beckmann rearrangement crystallised from dilute methyl alcohol (charcoal) in colourless prisms m.p. 172° C.

Found	C 64·2	H 7·3	N 5·2
Calc. for $C_{15}H_{21}NO_4$	C 64·5	H 7·5	N 5·

Hydrolysis of this amide with various strength alcoholic potash yielded only a very small amount of an amine insufficient for analyses and conversion back to the amide. The difficulty of hydrolysis was apparently due to the steric effect of the two ortho substituent groups.

Tetrahydro-benzylidene-evodionol (7-*hydroxy*-5-*methoxy*-6-*β*-*phenylpropionyl*-2 : 2-*dimethyl-chroman*).

Benzylidene-evodionol (1 grm.) dissolved in alcohol (20cc.) was reduced with hydrogen under two atmospheres pressure using platinum oxide as a catalyst. When the intense red colour of the solution had disappeared the solution was filtered and poured into water. The resulting tetrahydro-benzylidene-evodionol separated from

alcohol in white needles m.p. 88° C. With ferric chloride it gave a reddish-brown colour. It was completely insoluble in 1% caustic soda solution. The same substance was obtained by reducing benzylidene-dihydro-evodionol.

Found	C 74·1	H 7·3
Calc. for $C_{21}H_{24}O_4$	C 74·1	H 7.1

Hydrolytic action of concentrated alkali on tetrahydro-benzylidene-evodionol.

Tetrahydro-benzylidene-evodionol (1 grm.) was heated in a sealed tube with 40% alcoholic potash (20cc.) for half an hour at 230-250° C. The reaction mixture was poured into water, acidified and extracted several times with ether. The ether extract was washed with sodium bicarbonate solution and 1% aqueous caustic soda. The latter extract was acidified, extracted with ether, the ether solution dried and distilled. The residue which slowly solidified was crystallised from methyl alcohol and melted at 103° C. This is the melting point recorded by George and Robertson (*loc. cit.*) for 7-hydroxy-5-methoxy-2 : 2-dimethyl-chroman.

Found	C 69·	H 7·5
Calc. for $C_{12}H_{16}O_3$)	C 69·2	H 7·7

Acidification of the bicarbonate extract followed by thorough extraction with ether yielded a small amount of an acid m.p. 47° C. identified as β-phenyl-propionic acid by mixed melting point determinations.

Tetrahydro-benzylidene-methyl-evodionol (5 : 7-*dimethoxy*-6-β-*phenyl-propionyl*-2 : 2-*dimethyl-chroman*).

Reduction of benzylidene-methyl-evodionol or benzylidene-dihydro-methyl-evodionol with hydrogen and platinum oxide as above yielded tetrahydro-benzylidene-methyl-evodionol as an oil which could not be induced to crystallise. It readily formed an axime which on crystallisation from methyl alcohol melted at 129·5° C. This is the melting point recorded for the oxime of 5 : 7-dimethoxy-6-β-phenyl-propionyl-2 : 2-dimethyl-chroman by Backhouse and Robertson[8].

Pyrolysis of the dibasic acid $C_{15}H_{18}O_8$ (*evodionic acid*).

Evodionic acid was submitted to pyrolysis at 140-150° C. as described in the previous paper[1]. The solid product m.p. 185° C. (previously recorded 184° C.) which was separated from the other products by its insolubility in bicarbonate solution was re-examined.

Found	C 61·8	H 6·3
Calc. for $C_{10}H_{12}O_4$	C 61·2	H 6·1

It was identified as 4-hydroxy-2 : 6-dimethoxy-acetophenone (1) by conversion to O-trimethyl-phloracetophanone by means of dimethyl sulphate and by comparison with an authentic sample prepared by the method of Canter, Curd and Robertson (*loc. cit.*).

The glassy mass obtained by extraction of the melt with bicarbonate followed by acidification was esterified with methyl alcohol and sulphuric acid. The product was poured into water and extracted with ether. The ether extract was washed with sodium carbonate solution, sodium hydroxide solution and water and then dried over anhydrous sodium sulphate. On distillation of the ether the residual ester solidified and after crystallisation from light petroleum melted at 76° C. It was identical with the mono-methyl ester formed by direct esterification of evodionic acid recorded in the previous paper (*loc. cit.*). The caustic soda wash gave a trace of

a phenol. When the pyrolysis was carried out at 250° C. considerably more phenol was obtained. This phenol on methylation with dimethyl sulphate gave O-trimethyl-phloroglucinol m.p. 51-52° C.

Hydrolytic fission of evodionol with concentrated alkali.

Following the procedure of Bell, Robertson and Subramaniam evodionol (2 grms.) was refluxed with 25% caustic soda for one hour. The aqueous solution was then distilled with the constant addition of water to maintain the original volume. The aqueous distillate was treated with 2: 4-dinitro-phenyl-hydrazine hydrochloride and yielded a hydrazone which after several crystallisations from alcohol melted at 126° C. undepressed when mixed with a specimen sample of acetone-2 : 4-dinitro-phenyl-hydrazone.

Ozonolysis of methyl-evodionol. Methyl-evodionol (4 grms.) in carbon tetrachloride (40cc.) was treated with ozone-oxygen mixture until no more ozone was absorbed. The solvent was distilled off at 50° C. under reduced pressure and the residue decomposed with boiling water (30 cc.) in the presence of zinc dust (1 grm.), a little silver nitrate and hydroquinone after the method of Whitmore and Church[17]. After working up the product in the usual way a phenol was obtained from the alkaline wash which crystallised from methyl alcohol in yellow needles. It melted at 76-77° C., reduced ammoniacal silver nitrate and gave a brilliant red colour with ferric chloride. Its 2 : 4-dinitro-phenyl-hydrazone melted at 165° C.

Found	C 57·7	H 5·6
Calc. for $C_{11}H_{12}O_5$	C 58·9	H 5·4

The analytical figures for this substance are not good. There is little doubt however that this is the correct formula, for the final product of a series of reactions on it was identified and the intermediate products all gave satisfactory analytical figures.

This phenolic aldehyde (13) was methylated with methyl iodide and potassium carbonate in acetone for four hours. The acetone was distilled off, water added and the product extracted with ether. The ether extract was washed with dilute caustic soda solution and water and dried with anhydrous sodium sulphate. This yielded a white solid which crystallised from benzene-light petroleum in small prisms m.p. 84° C. It gave no colour with ferric chloride.

Found	C 60·7	H 6·2
Calc. for $C_{12}H_{14}O_5$	C 60·5	H 5·9

Oxidation of this methyl ether (·5 grm.) in acetone (20cc.) with 3% aqueous permanganate was carried out at 60° C. The solution was then decolourised with sulphur dioxide, made alkaline with caustic soda, extracted with ether, acidified with sulphuric acid and again extracted with ether. This extract yielded a crystalline acid (14) m.p. 149-150° C. (decomp.) after crystallising from benzene.

Found	C 56·2	H 5·7
Calc. for $C_{12}H_{14}O_6$	C 56·7	H 5·5

This acid was heated in a tube in an oil bath maintained at 160° C. for one hour. The product crystallised from light petroleum in needles m.p. 103° C. undepressed when mixed with an authentic sample of 2 : 4 : 6-trimethoxy-acetophenone.

Synthetic preparation of α (3 : 5-dimethoxy-phenoxy)-isobutyric acid.

O-dimethyl-phloroglucinol (5 grms.), prepared by the method of Robertson and Subramaniam[13], was dissolved in alcohol (20cc.) in which was dissolved sodium

(·8 grm.). To this was added methyl α-brom-isobutyrate (5 grms.). The mixture was allowed to stand overnight and was then gently refluxed for six hours. It was poured into water and thoroughly extracted with ether. The ether solution was washed with dilute sodium carbonate and sodium hydroxide solutions and finally with water. Removal of the ether left an ester which was immediately hydrolysed with alcoholic potash. Acidification of this alkaline solution yielded the acid α- (3 : 5-dimethoxy-phenoxy)-isobutyric acid (19) which was filtered off. It crystallised from light petroleum in colourless needles m.p. 74° C. (Yield 2 grms.) It was recorded in the previous paper[1] that sodium amalgam treatment of the bromo acid $C_{12}H_{14}O_5Br_2$ obtained by the action of hypobromite on evodionic acid, yielded an acid $C_{12}H_{16}O_5$ m.p. 74° C. This acid gave no depression when mixed with the synthetic α- (3 : 5-dimethoxy-phenoxy)-isobutyric acid.

Decarboxylation of α (3 : 5-dimethoxy-phenoxy)-isobutyric acid.

This experiment was carried out using both the synthetic acid above and the acid from the degradation of evodionic acid with the same results, thus giving further proof of their identity. The acid (1 grm.) was thoroughly mixed with excess powdered soda lime and heated directly with a burner. The oily aqueous distillate was extracted with ether and the ether dried and distilled. The residue (·01 grm.) after distillation under reduced pressure partially solidified in the refrigerator. This was dried on a porous plate and the solid crystallised from dilute alcohol. It melted at 51-52° C. and admixture with a sample of O-trimethyl-phloroglucinol caused no depression.

Thus decarboxylation was accompanied by loss of two carbon atoms resulting in the formation of a new methoxyl group. The bulk of the product of the reaction, however, was an oil which was probably the normal decarboxylation product, 1 : 3-dimethoxy-5-isopropoxy-benzene. This substance prepared by the condensation of isopropyl iodide and O-dimethyl-phloroglucinol with potassium carbonate in acetone was obtained as an oil which would not crystallise. A small yield of O-trimethyl-phloroglucinol was also obtained by submitting α-(3 : 5-dimethoxy-4-acetyl-phenoxy) isobutyric acid to the same drastic treatment with soda lime.

Synthetic Preparation of the methyl ester of α-(3 : 5-dimethoxy-4-acetyl-phenoxy)-isobutyric acid.

This ester was prepared by refluxing a mixture of 4-hydroxy-2 : 6-dimethoxy-acetophenone (1 grm.) and methyl α-brom-isobutyrate (1 grm.) in acetone (20cc.) in the presence of potassium carbonate. After ten hours most of the acetone was distilled off and ether added to the residue. The ether was washed with dilute caustic soda solution, then water and dried. This ether solution yielded a crystalline ester (·05 grm.) m.p. 76° C. identical with the mono-methyl ester formed by esterification of evodionic acid. (*See* previous paper[1].)

Oxidation of benzylidene-dihydro-methyl-evodionol.

Benzylidene-dihydro-methyl-evodionol (2 grms.) in acetone (50cc.) was treated slowly with 4% aqueous permanganate until the oxidation was complete. Sulphur dioxide was then passed in to dissolve the manganese dioxide. After the addition of dilute sulphuric acid the solution was thoroughly extracted with ether. The ether solution was washed with dilute sodium carbonate which in acidification and extraction with ether yielded a mixture of acids. This mixture was submitted to steam distillation to remove benzoic acid. The residue in the flask deposited a crystalline acid after cooling which melted at 169° C. (decomp.). Yield ·3 grm.

Found	C 60·9	H 5·8
Calc. for $C_{15}H_{18}O_6$	C 61·	H 6·1

This acid gave a precipitate with 2 : 4-dinitro-phenyl-hydrazine and since it is formed from the benzylidene derivative above together with benzoic acid it must clearly be represented by formula (22).

In another experiment the mixture of benzoic acid and acid (22) was not isolated with ether but was submitted to steam distillation in the presence of sulphuric acid. An oily neutral product was obtained in the distillate and no organic acid remained in the flask. The oily neutral product had no reactive groups and analytical figures indicated it to be 5 : 7-dimethoxy-2 : 2-dimethyl-chroman (23).

Found	C 70·2	H 8·0	OMe 27·
Calc. for $C_{13}H_{18}O_3$	C 70·3	H 8·1	OMe 27·9

This was confirmed by the preparation of the 8-formyl derivative by the Adams, Levene modification of the Gattermann aldehyde synthesis[18]. The chroman (·5 grm.) was dissolved in dry ether (20cc.) and to this was added zinc cyanide (·4 grm.). The mixture was cooled and saturated with dry hydrogen chloride and allowed to stand overnight. The solid material was filtered off, washed with ether and hydrolysed with hot water. The 5: 7-dimethoxy-8-formyl-2: 2-dimethyl-chroman was extracted with ether and converted half into its semicarbazone m.p. 217° C. and half into its 2 : 4-dinitro-phenyl-hydrazone m.p. 242° C. (Compare Robertson and Subramaniam)[13].

Formation of flavanones from benzylidene derivatives of evodionol and dihydro-evodionol.

Benzylidene-evodionol (2 grms.) was dissolved in alcohol. To this was added 10% sulphuric acid (30cc.) and the mixture boiled. Just sufficient alcohol was added to keep the benzylidene-evodionol in solution while being gently refluxed. Boiling was continued for twelve hours. On cooling a mixture of pale yellow and red crystals separated. The red benzylidene-evodionol was readily dissolved in a small volume of alcohol and the residue of 5-methoxy-8 : 8-dimethyl-1 : 2-pyrano-[3, 2, g]-flavanone was recrystallised from more alcohol from which it separated in pale yellow needles m.p. 126° C.

Found	C 75·2	H 6·0
Calc. for $C_{21}H_{20}O_4$	C 75·	H 5·9

In the same way benzylidene-dihydro-evodionol yielded 5-methoxy-8 : 8-dimethyl-6 : 7-dihydro-1 : 2-pyrano-[3, 2, g]-flavanone (25). The unchanged benzylidene-dihydro-evodionol was separated from the flavanone by washing with a small volume of alcohol. The flavanone crystallised from alcohol in colourless needles m.p. 145-146° C.

Found	C 74·4	H 6·4
Calc. for $C_{21}H_{22}O_4$	C 74·6	H 6·5

Synthesis of 5-hydroxy-7-methoxy-6-acetyl-2 : 2-dimethyl-chroman and dihydro-methyl-evodionol.

The preparation of 5: 7-dihydroxy-2: 2-dimethyl-chroman was carried out following the procedure of Bridge, Heyes and Robertson[15] in which the corresponding chromanone was reduced by Clemmenson's method. The $\beta\beta$-dimethyl-acrylic acid necessary for the preparation of the chromanone was prepared by the method of Barbier and Léser[16] in preference to that recommended by Bridge, Heyes and Robertson. It has the advantage of avoiding the use of the unpleasant α-brom-iso-valeric acid and also of avoiding the fractional distillation of the final product. The method consists of oxidising mesityl oxide with sodium hypochlorite. After destroying excess hypochlorite with sulphur dioxide the $\beta\beta$-dimethyl-acrylic acid separated in practically pure form on acidifying with sulphuric acid. After one crystallisation from light petroleum it melted at 69° C.

For the formation of the chromanone the procedure adopted by Bridge, Heyes and Robertson (*loc. cit.*) was followed closely. Variations in the relative quantities of the reagents adversely affected the yield of chromanone. The yields of both chromanone and chroman recorded by the Liverpool workers were readily reproduced. The introduction of the acetyl group in position 6 was accomplished by the Hoesch method adopted by Backhouse and Robertson[8]. The separation of 5 : 7-dihydroxy-6-acetyl-2 : 2-dimethyl-chroman from the isomeric 5 : 7-dihydroxy-8-acetyl- 2 : 2-dimethyl-chroman was brought about by a modification of their procedure. It was found that by careful fractional crystallisation from dilute methyl alcohol the 6-acetyl compound m.p. 229° C. separated first and the 8-acetyl derivative m.p. 150° C. was readily obtained from the mother liquor.

Methylation of 5 : 7-dihydroxy-6-acetyl-2 : 2-dimethyl-chroman (·2 grm.) with methyl iodide in acetone in the presence of potassium carbonate during two hours gave rise to a mono-methyl ether (·1 grm.) extracted from the reaction mixture with dilute alkali. It formed pale yellow needles from dilute alcohol melting at 88° C. and gave a 2 : 4-dinitro-phenyl-hydrazone m.p. 192° C. It is thus not identical with dihydro-evodionol and must therefore be an isomer. It gives a positive result with 2 : 6-dibrom-quinone-chlorimide supporting the formula 5-hydroxy-7-methoxy-6-acetyl-2 : 2-dimethyl-chroman (7).

Found	C 67·4	H 7·0
Calc. for $C_{14}H_{18}O_4$	C 67·2	H 7·2

Complete methylation was effected by refluxing 5 : 7-dihydroxy-6-acetyl-2 : 2-dimethyl-chroman with dimethyl sulphate and potassium carbonate in acetone solution for twelve hours. The bulk of the acetone was distilled off and the residue, after the addition of a little water, extracted with ether. The ether was washed with dilute caustic soda solution then with water and dried. Distillation of the ether gave a solid residue which after crystallising from alcohol melted at 91° C. By mixed melting point determinations it was found to be identical with dihydro-methyl-evodionol.

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